Summary of Safety and Effectiveness

I. GENERAL INFORMATION

Device Generic Name:	Implanted, Non-Programmable, Infusion Pump
Device Trade Name:	Model 3000 Constant Flow Implantable Pump with Bolus Safety Valve
Applicant's Name and Address:	Arrow International 1600 Providence Highway Walpole, Massachusetts 02081
PMA Number:	P890055
Date of Panel Recommendations:	March 5, 1991
Date of Notice of Approval to the Applicant:	MAR 11 1996

II. INDICATIONS FOR USE

The Model 3000 Constant Flow Implantable Pump with Bolus Safety Valve is indicated for the continuous regional intra-arterial delivery of 2'-deoxy-5-fluorouridine (FUDR), heparinized saline, normal saline, and bacteriostatic water.

The approved labeling for FUDR stipulates the indications, contraindications, and warnings for use of the drug in the pump.

Bacteriostatic water or saline are to be used to achieve the desired concentration of FUDR.
Heparinized saline may be used during an interruption of FUDR therapy to maintain catheter patency.

III. DEVICE DESCRIPTION

The Model 3000 Constant Flow Implantable Pump with Bolus Safety Valve, hereafter called "Pump," is a disk-shaped, non-programmable, infusion pump designed to be implanted for the purpose of delivering a continuous flow of medication to a specific body site. It has a body 7.8 cm in diameter and 2.4 cm high. Located on its top side is a domed center septa port 1.0 cm high

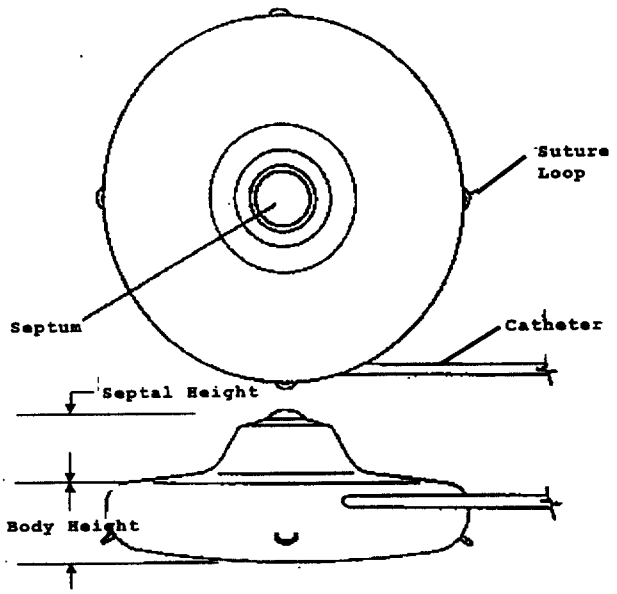

Figure 1. External Schematic of Model 3000 Pump

providing an overall pump height of 3.4 cm (see Figure 1). Once implanted, the Pump is accessed percutaneously through the center septa for purposes of both refilling the pump and providing a bolus injection. A silicone rubber outlet catheter (I.D. 0.6mm, O.D. 2.3mm) exits tangential from its edge. Four suture loops are spaced around the body of the Pump for securement.

The domed septa port houses two silicone rubber septa aligned vertically on center. A spacer is inserted between these septa creating an interseptal gap. This gap is the proximal end of the bolus pathway which leads from the interseptal gap directly to the outlet catheter bypassing the flow restricting mechanism of the pump (see Figure 2).

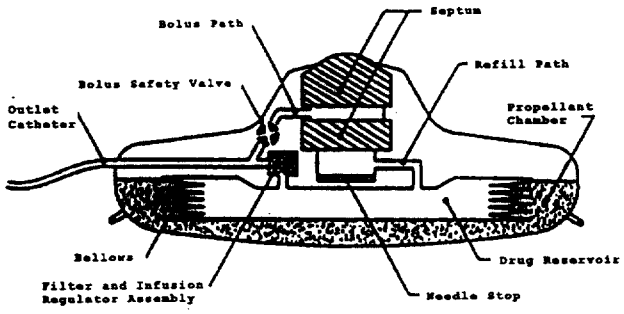

Figure 2. Cross-sectional Schematic

The Pump incorporates a valve, the Bolus Safety Valve, within the bolus pathway to prevent the administration of fluid through the pathway in the event the tip of a needle is positioned within the interseptal gap. This feature was added to an earlier version of the Pump in response to reports of inadvertent bolus events. The valve assembly consists of a valve spool, spring, and cup lever. The normal state of the valve is closed. When the Pump is accessed, the needle tip must pass through both septa and depress the cup lever in order for the valve to open.

The Pump body consists of a center plate to which have been welded upper and lower titanium shells called the upper cover and can, respectively. The space enclosed by the center plate and the can is divided into two chambers by a collapsible bellows. The interior chamber of the bellows is known as the drug reservoir. The volume of the drug reservoir is 30 ml. The second chamber formed by the exterior surface of the bellows and the can is known as the propellant chamber. The Pump is powered by a two-phase propellant.

When the Pump is implanted, the propellant exerts pressure on the exterior of the bellows at a temperature of 37°C. This pressure acts to collapse the bellows forcing the fluid contained in the drug reservoir through a filter plate, a capillary flow restrictor, and then through the catheter to the body (see Figure 2).

The flow restrictor consists of a capillary tube with an internal diameter of 0.05mm. The length of the tube is varied to obtain flow rates from 0.5 to 2.0 ml/day. Note, however, flow rate is also

dependent on temperature, altitude, and drug viscosity, as well as the pressure difference between the drug reservoir and the outlet pressure which depends on distal catheter placement.

Percutaneous access of the pump for a refill or bolus injection is accomplished in the same manner; however, a specific needle is necessary to perform each procedure successfully. When accessing the Pump to refill the drug reservoir, a standard 22 gauge non-coring needle is used. This needle has an opening at the most distal portion of the needle shaft. When the needle is correctly positioned, both septa are penetrated and the needle tip is fully advanced until seated in the chamber below the lower septum. Thus, the opening of the needle is also contained in the chamber below the lower septum. This lower chamber directly communicates with the drug reservoir via a hole. Injection of fluid into this chamber fills the drug reservoir. Although correctly inserting the needle into the Pump to perform a refill does depress the cup lever and opens the bolus safety valve, the flow passages affected by the valve are not in the fluid path for normal pump refill. Therefore, in effect the valve serves no purpose during a refill procedure when it is correctly performed. In the event the refill needle is not inserted through both septa and stops within the interseptal gap, the valve remains closed preventing a direct infusion through the bolus pathway.

When accessing the Pump to perform a bolus injection, a special bolus needle is required. The tip of this needle is sealed, and an opening has been created partially down the needle shaft. When this needle is inserted through both septa and advanced to the needle stop, the needle opening aligns within the interseptal gap. Additionally, the needle tip depresses the cup lever opening the safety bolus valve allowing for direct communication with the outlet catheter. In this manner, injection of fluid into the interseptal space is delivered directly to the patient as a bolus injection.

Each Pump is packaged with one (1) 22 gauge non-coring needle, one (1) Special Bolus Needle, Instructions for Use, a Pump Implant Record, a Patient I.D. Card, a Patient Education Booklet, an O.R. Record, and a Physician Record.

A refill kit is available to aid in performing pump refills. This kit incudes one (1) 22 gauge non-coring needle attached to a 12" tubing set with one-way stopcock, a 35 ml syringe, an extra 22 gauge non-coring needle, a non-absorbent fenestrated drape, a plastic syringe cap, three (3) povidone-iodine swabsticks, two (2) alcohol prep pads, two (2) gauze pads, an adhesive dressing, a Patient chart sticker, and Instructions For Use.

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IV. CONTRAINDICATIONS

The Pump is contraindicated for use in patients with the following conditions:

1. Known or suspected infection, bacteremia, septicemia, or peritonitis.

2. Known experiences of allergic reaction or other signs of intolerance to implanted devices.

3. Emotional or psychiatric problems.

4. Those whose body size is insufficient to accommodate the physical size of the pump.

In addition, the contraindications specified in the approved drug labeling must be observed when using the drug product in the Pump.

V. WARNINGS

The Pump should be implanted and refilled only by qualified medical personnel, knowledgeable in the surgical use and servicing of implantable devices and catheters, and trained specifically to implant or refill the Pump. Use of the Pump by personnel not properly trained in its implantation and/or servicing may lead to serious consequences involving either under or over-delivery of drug to the patient. In the event of an over-delivery of drug refer to the approved drug labeling for appropriate action.

Utilization of the Pump requires the proper handling (filling, storage and dispensing) of a significant volume/dosage of drug. This amount of drug may be extremely harmful to the patient if delivered suddenly or inappropriately.

Bolus access and pump refill procedures must be performed using the correct access needle. Never attempt to refill the Pump using a Special Bolus Needle. This use will result in giving a bolus injection to the patient and may cause a fatal drug overdose.

VI. PRECAUTIONS

REGARDING THE USE OF THE PUMP

Never aspirate fluid from the Pump. Aspiration will cause blood to be drawn into the catheter and result in occlusion.

Only use Arrow Special Bolus or Arrow 22G Non-coring needles to access the pump septum. It is critical to the integrity of the pump septum that no other needles be used to penetrate the septum.

It is important to precisely follow the Pump refill instructions in order to successfully complete the Pump refill procedure. If the needle

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is not properly positioned, and verified as detailed in the Pump Refill Procedures, there is a possibility drug extravasation will occur.

Before performing a bolus injection of any drug, review all warnings, precautions, indications, and contraindications on the drug labeling.

Do not use a mechanical pressure injector system to accomplish a bolus procedure. Pressures should not exceed 40 psi when administering a bolus injection or infusion. For injections use only 10 ml (or larger) syringes and do not inject or infuse at a rate greater than 5 ml/min.

When the system is flushed with saline while performing a bolus procedure the patient will receive a bolus dose of drug equal to the volume of drug contained in the internal bolus pathway of the Pump, plus the volume of drug in the catheter. The volume of drug in the internal pathway of the Pump is 0.3 ml. The volume of the drug contained in the catheter is calculated by multiplying the length (in cm) of the catheter by 0.003 ml/cm.

INFORMATION FOR THE PATIENT

The patient should refrain from physical activity that may cause injury to the area near the pump implant site or the pump itself.

The patient should notify his or her physician immediately if any unusual symptoms are noticed.

The patient must return on established refill times to prevent the pump from running dry which might lead to thrombus formation at the catheter tip.

The patient should carry the Patient I.D. card in case of a medical emergency to alert health care workers of the presence of the pump.

The patient should contact their physician before traveling by air. Changes in ambient pressure affect pump flow rate which may lead to under or over-delivery of drug to the patient.

The patient should not use a heating pad over the pump site or take long hot baths or saunas. Elevated temperature and decreased ambient pressure will increase the flow rate of the pump which may lead to over-delivery of drug to the patient..

The patient should inform their physician if they have an increased body temperature. Elevated body temperature will increase the flow rate of the pump which may lead to over-delivery of drug to the patient.

The patient should inform their physician if they move to a different altitude. Decreased ambient pressure will increase the flow rate of the pump which may lead over-delivery of drug to the patient.

The patient should be informed of the appropriate precautions listed in the drug labeling.

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The patient should be provided a Patient Education Booklet and the information contained in the booklet should be thoroughly understood by the patient prior to implantation.

The patient should remain still throughout a bolus infusion to prevent any movement of the Special Bolus Needle. If the needle is withdrawn an amount exposing the lumen above the upper septum of the Pump, drug extravasation may occur.

VII. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives to use of the pump to deliver the drug solutions previously described are as follows:

1. Intermittent injection of the drug solution into the vascular system via a needle and syringe.

2. Continuous parenteral administration of the drug solution through an I.V. set and catheter utilizing either gravity or an external infusion pump.

VIII. MARKETING HISTORY

The Pump has never received marketing approval in the United States. An earlier version of the Pump which did not contain the Bolus Safety Valve was marketed in Germany, Spain, France, the Netherlands, Belgium, and Denmark during the period January 1990 through May 1991. This version of the Pump was withdrawn from these markets after reported incidents of inadvertent bolus administration of drug products to patients through the pump bolus pathway.

Since March 1993, the Pump has been marketed in Germany and Canada. One adverse event involving a device failure has been reported. A post explant failure analysis report for this device indicated the capillary tube contained in the Pump was damaged during a weld procedure. Appropriate action has be taken to correct this situation.

IX. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The potential adverse effect of the device is as follows:

Device failure - A device failure would require a corrective surgical procedure. In addition, the failure would result in either a stoppage of the medication flow or an amount of the medication escaping into the subcutaneous tissue.

Other potential complications are as follows:

1. Catheter thrombosis (occlusion) - This can occur if the pump

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becomes empty, flow stops, and the blood enters the catheter. Catheter occlusion could also occur during the surgical procedure by tying the sutures too tight and ligating the catheter. This might necessitate a surgical procedure to relax the sutures to regain flow.

2. Infection - This can be associated with the implantation procedure, the device, or the refill procedure and may involve the pump reservoir, catheter, or pump pocket. This might necessitate the explantation of the device to clear the infection.

3. Catheter migration - If the catheter migrates because of rigorous exercise, the patient would receive the medication in a different area of the body. This might necessitate a surgical procedure to reposition the catheter for proper therapy.

4. Skin necrosis - If the skin over the implanted device is sutured too tightly then skin necrosis could occur. This might necessitate a surgical procedure to reposition the pump in another location of the body.

5. Drug extravasation - This could occur if drug is accidentally spilled into the pump pocket during the refill procedure. This might necessitate temporary discontinuation of therapy.

6. Catheter shear - If the catheter is positioned too close to the clavicle and first rib during implantation shearing of the catheter may occur. This might necessitate a surgical procedure to replace the catheter.

7. Bolus path occlusion - This results from the injection of particulate solutions through the bolus pathway and incompatibilities between a bolus solution and the pump materials. This may be resolved by flushing the bolus pathway, but might require a surgical procedure to replace the pump and/or catheter.

8. Pump dislodgement - This could occur if a securement suture breaks or the patient participates in rigorous physical activity. This might necessitate a surgical procedure to reposition or attach the pump.

9. Catheter leakage - This can be associated with the implantation procedure, refill procedure, or catheter breakage. This results in the delivery of drug to an area of the body other than the intended site. This requires a surgical procedure to replace or repair the catheter.

10. Bolus injection error - This can be associated with an incorrect selection of the access needle during a refill or bolus procedure. Selection of the incorrect needle may result in the injection of a significant volume/dosage of drug to the patient. This amount of drug may be extremely harmful to the patient if delivered suddenly or inappropriately.

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X. SUMMARY OF STUDIES

A. In Vitro Studies

Testing was conducted to characterize the mechanical performance and biological reactivity of the components of the Pump.

1. Bellows Tests

Tests were conducted which demonstrated the bellows would a) effectively transmit the pressure of the propellant, b) maintain a liquid and vapor impermeable barrier over the life of the device, and c) hold 30 ml of drug and remain in the allowable design envelope.

2. Catheter Tests

Catheter Joint Integrity. The connection of the catheter to the Pump was tested for its ability to withstand an axial load. Catheter joints on fully assembled Pumps were subjected to an increasing axial load to failure. Failure of test units occurred at loads ranging from 3.1 to 3.7 lbs.

Catheter Material Integrity. The integrity of the catheter material was characterized using a tensile load test. Segments of the catheter material were subjected to an increasing tensile load to failure. Tested catheters failed at loads ranging from 5.0 to 5.4 lbs.

Catheter Burst Tests. Catheters were tested to assess their ability to withstand internal operating pressures. Catheters were subjected to increasing internal pressure until rupture. Tested catheters ruptured at 130 to 135 psi.

3. Septum Tests

Septum Puncture Life Test. Testing was conducted to determine the puncture life of the septum material. Sub-assemblies consisting of upper and lower septa installed in the septa assembly housing were repeatedly punctured both with 22 gauge non-coring needles and special bolus needles at a ratio of 50 to 1, respectively. Septa leakage was evidenced by the formation of air bubbles when the sub-assembly was submerged in bacteriostatic water and the interseptal gap was pressurized to 40 psi. All septa performed beyond the design life of 1500 punctures.

Septum Proof Pressure Test. Testing was conducted to determine the ability of the septum material and septum assembly to withstand internal operating pressures. Septa were installed into pump sub-assemblies and subjected to 200 psi internal pressure. In all units tested, the septa remained in place and did not blow out of the sub-assembly. No leaks were observed.

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Suture Loop Pull Test. Testing was connected to assess the integrity of the suture loop and joint. Suture loops were subjected to 10 lbs loads in each of five directions. No evidence of failure was seen under 30X magnification.

4. Bolus Safety Valve Tests

Bolus Safety Valve Function Test. The Bolus Safety Valve Function Test evaluated the ability of the valve system to withstand a pressure of 40 psi in the normal closed state and permit fluid flow through the bolus pathway during a simulated bolus injection. This test was performed subsequent to stress or wear inducing states (e.g., thermal cycling, shock, sterilization, etc.) in order to verify the states' impact on valve function.

Product Sterilization. Testing was conducted to assess the effect of steam sterilization on the performance of the valve assembly. Assembled Pumps were subjected to 2 or 6 production steam sterilization cycles. After all sterilization cycles were completed, each unit was subjected to a Bolus Safety Valve Function Test. The valves in all units withstood a pressure of 40 psi in the normal closed state and permitted fluid flow through the bolus pathway during a simulated bolus injection.

Shock Test. Testing was conducted to assess the effect of shock loads on the performance of the valve assembly. Assembled Pumps were dropped from a height of 3 feet onto a concrete floor covered with 1 inch plywood. Each Pump was subjected to 6 impacts along an x-y-z coordinate system established at the pump center. After the application of all shock loads, each pump was subjected to a Bolus Safety Valve Function Test. All units withstood a pressure of 40 psi in the normal closed state and permitted fluid flow through the bolus pathway during a simulated bolus injection.

Thermal Cycling. Testing was conducted to assess the effects of thermal cycling on the performance of the valve assembly. Assembled Pumps with flow pathways filled with bacteriostatic water were subjected to 4 thermal cycles each consisting of 24 hours at -17°C and 24 hours at 21°C. After thermal cycling, each pump was subjected to a Bolus Safety Valve Function Test. All units withstood a pressure of 40 psi in the normal closed state and permitted fluid flow through the bolus pathway during a simulated bolus injection.

Bolus Safety Valve Proof Pressure. Testing was conducted to assess the ability of the valve system to withstand internal operating pressures. A non-coring needle was inserted into the interseptal gap of assembled units. The interseptal gap was subjected to 25 pressurization cycles covering atmospheric pressure to 200 psi back to atmospheric pressure. During cycling, the outlet catheter of each unit was monitored for fluid flow indicating flow through the bolus pathway. No fluid flow was observed from any pump. After all pressure cycles, each pump was subjected to a Bolus Safety Valve Function Test. All units withstood a pressure of 40 psi in the normal closed state and permitted fluid flow through the bolus pathway during a simulated bolus injection.

Bolus Safety Valve Cycling Test. Testing was conducted to assess the performance of the valve assembly over the design life of the Pump. Units were repeatedly punctured with a 22 gauge non-coring needle. Valve operation was verified by the appearance and cessation of air bubbles at the tip of the outlet catheter when the interseptal gap was pressurized to 2 psi. After every 250 punctures or the observance of any anomalous performance, a Bolus Safety Valve Function Test was performed on each unit. All units performed beyond their design life of 1500 septa punctures.

Valve Gland Cycle Test. The valve gland consists of 2 O-rings which seal the moveable shaft of the valve spool acting as a barrier between the bolus pathway and the drug reservoir. Testing was conducted to assess the performance of the valve gland over the design life of the Pump. Sub-assemblies of the valve gland were cycled duplicating the action of the valve components during a refill or bolus procedure. Periodic leak tests were performed by pressurization with 10 psi air. Failure was evidenced by bubble formation. All sub-assemblies performed beyond the design life of 1500 cycles.

5. Filter Tests

Bubble point tests were performed on filter sub-assemblies to determine the pore size of the filter material. Test results indicated the filter material had no pores greater than 0.2 μm in diameter.

6. Capillary Joint Tests

Testing was conducted to assess the ability of the capillary joint to withstand high pressure and repeated autoclave cycles. No test articles showed an incidence of failure when pressurized to 160 psi. Joints failed under axial loads of 0.8 to 1.0 lbs.

7. Shelf Life Tests

Testing was conducted to assess the ability of the package material to maintain device sterility over time. Test data demonstrated the ability of the package material to maintain sterility at a two year test point.

8. Flow Testing.

Testing was conducted to verify the ability of the Pump to deliver fluid at a constant flow rate over time. Assembled units were flow tested at a temperature of 37°C ± 0.01°C using both bacteriostatic water and a mixture of FUDR (20 mg/ml) and heparin (2000 U/ml). Flow variations from mean flow rates were attributed to the bellows spring rate. No pump rapidly expelled its reservoir contents.

9. Shock and Vibration Tests.

Testing was conducted in accordance with the National Safe and Transit

Association (NSTA) Preshipment Test Procedure (April, 1991) to assess the effects of shock and vibration under simulated shipping conditions on the performance of the Pump. Packaged and unpackaged units were tested.

Flow tests were performed pre- and post-shock and vibration conditioning. A calibration flow cycle using bacteriostatic water was used to measure changes in performance. No differences in flow rate for unpackaged units were noted. Packaged units exhibited a decrease in flow rate of 0.02 ml/day.

Leak testing was performed pre- and post-shock and vibration conditioning to test for the presence of propellant leaks. No leaks were detected.

10. Biocompatibility Studies.

Testing was conducted to assess the biocompatibility of the pump materials. All blood and tissue contacting materials were tested in accordance with relevant sections of the U.S. Pharmacopeia and Tripartite Biocompatibility Guidance for Medical Devices (September, 1986). The biocompatibility of the pump materials is appropriate for the intended use.

11. Compatibility Tests

Testing was conducted to assess the compatibility between the pump fluid path materials and the indicated drug products. After incubation periods ranging from 43-50 days at 37°C±0.1°C, pumps were disassembled and examined microscopically for signs of degradation and corrosion. No foreign build-up nor signs of degradation were observed.

12. Stability Tests

Tests were conducted to assess the stability of the indicated drug products when contained in the Pump. The stability of heparin alone (1000 U/ml and 10000 U/ml) and heparin in combination with FUDR (1000 U/ml heparin, 1.0 mg/ml FUDR) was studied when contained in assembled units for periods ranging from 42 to 50 days incubated at 37°C. Eluant catheter and drug reservoir samples were collected over the incubation period. FUDR concentration was determined using a suitable HPLC method. Heparin concentration was determined using the Thrombin Clotting Time assay.

The test data indicate that heparin alone and in combination with FUDR is stable in the Pump at 37°C over a 6-7 week period.

B. Animal Studies

Two animal studies were conducted to evaluate the *in vivo* performance of the Pump for the infusion of FUDR prior to initiation of studies in human subjects. Between July 16, 1987 and October 21, 1987, five (5)

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Pumps of the earlier version were implanted in four (4) mixed-breed hounds. Catheters were placed in the common hepatic artery. A two week infusion of FUDR was alternated with a two week infusion of heparinized saline (1000 U/ml). FUDR infusion was discontinued when the development of hepatoxicity was evidenced by increases in levels of serum glutamic-pyruvic transaminase (SGPT) and alkaline phosphatase.

Total pump experience consisted of 485 implant days. Average implant duration was 92 days. Average flow rates were 0.81±0.16, 0.77±0.17, 0.88±0.04, and 0.67±0.11 ml/day. One device failure (i.e., stoppage of flow) was observed after one flow cycle. Post-explant analysis indicated damage to the flow restrictor was present preventing drug delivery from the reservoir of the pump to the outlet catheter. No other device complications were reported.

All dogs receiving FUDR therapy presented with hepatoxicity during the investigation. This was attributed to a refined catheter placement technique which led to drug infusion consistently with a majority of the liver.

On November 9, 1992, two (2) Pumps of the modified version were implanted one in each of 2 mixed-breed hounds for 105 days each. During this time, the bolus chambers of each pump were accessed every 3 to 4 days using a special bolus needle. Each pump was also refilled with 30 ml of heparinized saline (1000 U/ml) every 14 days using a 22 gauge non-coring needle. A combined total of 65 bolus accesses and 16 pump refills were performed. The average flow rates observed for each pump were 1.55±0.20 ml/day (range: 1.29-1.9 ml/day) and 1.80±0.22 ml/day (range: 1.3-2.0 ml/day). The following adverse events were observed: 1 catheter occlusion and 2 pump dislogdements. At the time of pump explant, both pump pockets were free of infection. No edema was reported.

Based on these results, the Pump was considered reasonably safe for implantation in human subjects.

C. Clinical Studies

A clinical evaluation was conducted to assess the ease of use, safety and reliability of the pump for the delivery of FUDR and other associated fluids.

Description of Patient Population

Eighty-two (82) patients were enrolled in the study at nine (9) investigational centers. Approximately equal numbers of males (46) and females (36) were included, ranging in age from 30 to 84 years with a mean age of 61 years. Patients had metastatic liver cancer. Patients with extrahepatic metastases were excluded unless the metastases could be surgically removed or effectively irradiated.

Pump Experience

Sixty-two (62) patients were implanted with 64 Model 3000 pumps of the initial version between June 1, 1988 and April 15, 1991. These pumps were implanted for a total of 1,069.35 patient months. Average patient follow-up was 525 days (range: 16 to 1688). During follow-up, 1,950 pump refill and 286 bolus access procedures were performed.

Twenty (20) patients were implanted with 21 Model 3000 Pumps With Bolus Safety Valve between December 15, 1993 and February 15, 1995. The principle difference between the initial version of the Model 3000 pump and the Model 3000 Pump With Bolus Safety Valve was the incorporation of the bolus safety valve in the bolus fluid pathway. This modification had no observable effect on the continuous flow operation of the Pump. These pumps were implanted for a total of 139.99 patient months. Average patient follow-up was 250 days (range: 36 to 400). During follow-up, 285 pump refill and 47 bolus access procedures were performed.

Combined pump experience was gathered over a total of 1,209.34 patient months. Average patient follow-up was 433 days. Two thousand two hundred thirty-five (2,235) pump refill and 333 bolus access procedures were performed.

Pump Performance

Safety and efficacy of the Pump was assessed based on complication rates and *in vivo* flow rate measurements. Objective response to therapy, drug toxicity data, and patient survival rates were evaluated as supportive information.

1. *In Vivo* Flow Rates

FUDR therapy consisted of a 14-day, on-off cycle of FUDR and heparinized saline, and continued unless tumor progression was evident or grade 4 toxicity was noted. *In vivo* flow rates of each pump were measured at pump refills. The data were analyzed to determine flow accuracy and consistency over time. Pumps exhibited early elevated flow rates over the first few pump cycles. This has been attributed to elevated pump pocket temperature post implant. A 95% confidence interval for average normalized flow was constructed. Pumps exhibited an average *in vivo* flow rate error of +1.9% (S.D. = 16.1%). Based on patient response, survival rates, and drug toxicity data, this variation was not considered clinically significant for the delivery of FUDR. Measurement error was identified as the largest contributor to the variation in flow rate error. Measurement errors of *in vivo* flow rates were estimated to range from 14% to greater than 200%. The average measurement error excluding flow cycles where the percent error was greater than 50% was estimated as 24.5%.

Pump flow consistency over time was evaluated using the von Neumann statistic to test for randomness in flow rate fluctuation.[1,2] Of the 85 pumps implanted, 81 pumps were evaluated using the von Neumann statistic. Two pumps were unevaluable due to early device failures

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(i.e., no flow). One pump was unevaluable due to patient expiration shortly after implant unrelated to the device and 1 pump was unevaluable due to an hepatic artery thrombosis shortly after implant. Fourteen (17.3%) of the 81 evaluated pumps showed a statistically significant long-term trend in flow rate either in an excessive up and down fashion or in a form of steady decline ending in a rapid drop. Based on clinical outcomes, these trends were not considered clinically significant for the delivery of FUDR.

2. Complications

Constant Flow Operation. Adverse reactions and complications observed during the clinical study are as follows: pump failure (2), bolus path occlusion (4), cannula dislodgment (2), cannula erosion (1), cannula leakage (2), cannula occlusion (2), contaminated pump reservoir (1), drug extravasation (3), febrile response (1), hepatic artery thrombosis (1), catheter infection (1), pump pocket infection (1), pump dislodgement (4), recurrent hematoma (1), seroma (1), bolus injection error/training error (1), partial catheter occlusion (1), and FUDR toxicity (43). Table 1 separates the events as device related or user/procedure related, and compares the experience with the initial version of the Pump to that of the modified version. Drug toxicity is addressed below.

Complication	Initial Version of Pump	Modified Version of Pump
Device Related	0.18	0
User/Procedure Related	2.12	2.83
Overall	2.12	2.83

Table 1. Complication rates are given as percent complications per patient month.

Two (2) device failures occurred early in the clinical study. In each of these cases a pump was implanted before proper flow was initiated. Subsequently, neither pump flowed in-vivo. This problem was corrected by a modification to the flow restrictor combined with the addition of more precise Instructions for Use.

One pump was explanted due to stoppage of flow after the injection of an imaging agent (TCC-99 MAA HAPS) through the bolus pathway. Post-explant analysis of this pump found the pump to be operating within specifications. However, particle masses collected from the catheter suggested a partial catheter occlusion was present. The particles were analyzed and found to be denatured protein.

Bolus Path Access. Although not reported in this clinical study, the adverse event "Inadvertent Bolus of Drug" was observed in another study investigating the use of the initial version of the Pump. Since the Pump has been modified to incorporate the Bolus Safety Valve, no events of this type have been observed.

However, one adverse event labeled "Bolus Injection Error/Training Error" has been observed with the use of the modified version of the Pump. This event involved the inadvertent use of a 22 gauge non-coring needle when attempting to perform a bolus injection. The drug to be bolused was added to the contents of the pump reservoir.

Table 2 provides a comparison of the complication rates associated with the use of the bolus pathway in the initial version of the Pump and the modified version of the Pump.

	Initial version of Pump (% compl./access)	Modified Version of Pump (% compl./access)
Device Related	0	0
User/Procedure Related	0.35	2.13
Total	0.35	2.13

Table 2. Bolus Path Access Complication Rates

The adverse events and complication rates reported in the clinical study are comparable to events observed with other commercially available implantable pumps. These event rates are acceptable for the indications for use of the device.

3. Overall Objective Response to Therapy.

The overall objective response to therapy was graded as follows: 1) complete remission (CR): disappearance of all clinical evidence of tumor on physical examination, x-ray, scan, and biochemical evaluation greater than 1 month, 2) partial remission (PR): 50% decrease in the sum of the products of the perpendicular diameters of all measured lesions for greater than 1 month; no simultaneous increase in size of any lesions or appearance of new lesions may occur, 3) stabilization (SD): 50% decrease or 25% increase in measurable disease for greater than two months, and 4) progression (PD): 25% increase in measurable disease or the appearance of new lesions. Of the 82 patients, 71 were evaluable using the objective response criteria. Eleven patients were unevaluable due to complications (2) (e.g., hepatic artery thrombosis, cannula erosion), no FUDR therapy (4), or less than 4 months follow-up (5). No patients exhibited complete remission, as defined. Seven (7) patients or 8.5% showed a partial response. Twenty-five (25) patients or 30.5% exhibited stabilized disease. Thirty-nine (39) patients or 47.6% exhibited disease progression.

4. Drug Toxicity.

Table 3 summarizes the drug related toxicity events reported during the clinical study. These rates are comparable to those reported for similar implantable pumps.[3,4,5,6]

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Pump	# of Patients	Hepatic Enzymes Elevation	Gastric/Ulcer Disease	Diarrhea	Biliary Sclerosis	Elevated Bilirubin
Initial Version	62	42%	15%	2%	0%	3%
Modified Version	20	20%	0%	5%	0%	0%

Table 3. Drug Toxicity Rates. Rates given as percent events per patient.

5. Survival Rates.

Table 4 compares 1-year and 2-year patient survival rates in the clinical study with survival data collected in four (4) published clinical studies. The comparison demonstrates the data collected in the clinical study is consistent with that reported in the literature.

Study	Patient Implants HAI	>1 yr (12-24 mo.)	>2 yr (25-36 mo.)
M3000 initial version	62	60%	23%
M3000 modified version	20	n/a	n/a
MSKCC[3]	162	60%	25%
NCOG[4]	143	60%	30%
NCI[5]	64	85%	44%
France[6]	162	61%	20%

Table 4. Patient Survival Data

XI. CONCLUSIONS DRAWN FROM STUDIES

The information provided in the Premarket Approval Application is valid scientific evidence and provides reasonable assurance that the Model 3000 Constant Flow Implantable Pump with Bolus Safety Valve is safe and effective for the indications stated in Section II. The *in vitro* tests substantiate to a reasonable extent the specifications of the device. Various laboratory and animal tests demonstrate the device is biocompatible, non-pyrogenic and non-toxic. The results of the clinical studies indicate the device is safe and effective for the stated indications for use. Drug toxicity and patient survival rates reported when using this device for its indications are comparable to those reported in the literature for other commercially available implantable pumps. Two to three percent of the patients in the clinical study experienced complications that appeared to be related to the use of the investigational device.

The combined results of the laboratory, animal and clinical testing provide the requisite assurance of the safety and effectiveness of the device for the stated indications.

XII. PANEL RECOMMENDATIONS

The General Hospital and Personal Use Device Section of The General Medical Devices Panel met on March 5, 1991 to consider the safety and effectiveness of the Model 3000 Implantable Pump (initial version).

The panel recommended to CDRH that the PMA for the original version of the Model 3000 Implantable Pump be considered approvable with conditions.

XIII. FDA DECISIONS

The FDA disagreed with the Panel's recommendation in a letter to the applicant dated April 22, 1991. This decision was based in part on outstanding issues related to the clinical data, flow rate accuracy of the Pump, bolus function data, drug stability data, and the marketing history of the Pump.

Shortly thereafter, FDA became aware of reports of inadvertent bolus events occurring with the use of the Pump.

On July 27, 1992, the applicant met with FDA and presented the modification to the Pump to incorporate the Bolus Safety Valve.

On December 1, 1994, the applicant amended the PMA with clinical data on the use of the modified version of the Pump.

On January 29, 1996, FDA issued an approvable letter requesting:

1. A justification for the selection of the exclusion criteria applied during the von Neumann statistical analysis of the pumps and completion of the von Neumann statistic calculations for pumps not yet evaluated;

2. Clarification of the pump packaging information and packaging and sterilization information for the Special Bolus Needle (Cat.# 4013), the Arrow Non-Coring Needle (Cat.# 4009), and Refill Kit (Cat.#7001);

3. Information on the marketing status and processing of the components contained in the Refill Kit (Cat.#7001);

4. A revised copy of the Instructions For Use to include the following changes:

    a. removal of the investigational use statement (21 CFR 812.5(a)) and inclusion of the prescription statement (21 CFR 801.109(b)(1)) where appropriate;

    b. removal of the following clause under DESCRIPTION: "materials recognized for their high degree of biocompatibility and long life;" and

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c. the inclusion of instructions which explain the use of the graphs provided on page 19 and how they relate to the arterial flow rate specified on the pump label;

d. Removal of the Patient Selection section and revision of the Contraindications section to include the following statements:

(I) FUDR should be used with added caution in patients with impaired hepatic or renal function; and

(ii) patients with known disease extending beyond an area capable of infusion should be considered for systemic therapy with other chemotherapeutic agents; and

5. Concurrence with, or suggested revision of, the "Conditions of Approval" and agreement to conduct the following:

a. a postapproval study to confirm the long term safety and effectiveness of the design and labeling modifications implemented to address early reports of inadvertent bolus administration of drug product to patients.

b. a postapproval study to establish the compatibility between the indicated infusates and the device materials over repeated pump refills for a minimum exposure period of 6 months.

c. a postapproval study to establish long term changes in flow variation (i.e., accuracy and consistency) under controlled laboratory conditions.

On February 6, 1996, the applicant amended the PMA satisfactorily suppling the information requested and agreeing to comply with the "Conditions of Approval" and to conduct the listed postapproval studies.

On September 13, 1995, the applicant's manufacturing facilities had been inspected and found to be in compliance with the Good Manufacturing Practices (GMP) regulations.

On MAR 11 1996, FDA issued an approval order to the applicant.

XIV. APPROVAL SPECIFICATIONS

The approval specifications are described in Section XIII and in the conditions of approval, and with addition of the following:

FDA restricts the sale, distribution, and use of this device to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device

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that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

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